PATENT COOPERATION TREATY

Reply due.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

DUE ON MAR 05 2006

To:
OGILVY RENAULT
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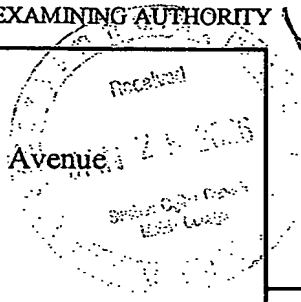

PCT

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rule66)

	Date of mailing *(day/month/year)* 19 January 2006 (19-01-2006)
Applicant's or agent's file reference 15922-3PCT	**REPLY DUE** within 1.5 months/~~days~~ from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2004/002070	02 December 2004 (02-12-2004)	05 December 2003 (05-12-2003)

International Patent Classification (IPC) or both national classification and IPC
IPC: A61K 41/00 *(2006.01)*, A61N 5/06 *(2006.01)*, A61K 35/14 *(2006.01)*, A61K 35/12*(2006.01)*, A61K 39/00*(2006.01)*,

Applicant
UNIVERSITE DE MONTREAL ET AL

1. [ ] The written opinion established by the International Searching Authority:
   [ ] is [ ] is not
   considered to be a written opinion of the International Preliminary Examining Authority.
2. This (first, etc.) opinion contains indications relating to the following items:
   - [X] Box No. I Basis of the opinion
   - [ ] Box No. II Priority
   - [X] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - [ ] Box No. IV Lack of unity of invention
   - [X] Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - [ ] Box No. VI Certain documents cited
   - [ ] Box No. VII Certain defects in the international application
   - [X] Box No. VIII Certain observations on the international application
3. The applicant is hereby **invited to reply** to this opinion.
   When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(e).
   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.
   Also For the examiner's obligation to consider amendments and/or arguments, see Rule *66.4bis*. For an informal communication with the examiner, see Rule 66.6. For an additional opportunity to submit amendments, see Rule 66.4.

   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary report on patentability (Chapter II of the PCT) must be established according to Rule 69.2 is: 14 April 2006 (14-04-2006)

Name and mailing address of the IPEA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Ryan Jaecques (819) 953-6570

WRITTEN OPINION OF THE
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International application No.
PCT/CA2004/002070

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of:

[ ] the international application in the language in which it was filed

[ ] a translation of the international application into , which is the language of a translation furnished for the purposes of:

[ ] international search (under Rules 12.3(a) and 23.1(b))

[ ] publication of the international application (under Rule 12.4(a))

[ ] international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this opinion has been established on the basis of *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."):*

[ ] the international application as originally filed/furnished

[X] the description:

pages	1, 3-15 and 17-21		as originally filed/furnished
pages	2 and 16	received by this Authority on	05 December 2005
pages		received by this Authority on	

[X] the claims:

pages			as originally filed/furnished
pages		as amended (together with any statement) under Article 19	
pages	22-51	received by this Authority on	05 December 2005
pages		received by this Authority on	

[X] the drawings:

pages	1-4		as originally filed/furnished
pages		received by this Authority on	
pages		received by this Authority on	

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages
[ ] the claims, Nos.
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

4. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

[ ] the description, pages
[ ] the claims, Nos.
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

[ ] the entire international application

[X] claims Nos. 1-12, 14-17, 32-43 and 45-49

because:

[X] the said international application, or the said claims Nos. 1-12, 14-17, 32-43 and 45-49
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

The subject matter of claims 1-12, 14-17, 32-43 and 45-49 relates to a method of medical treatment of the human or animal body under Rule 67.1 PCT. For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exists in the PCT. The patentability can also be dependent upon the formulation of the claims. Certain national offices do accept claims worded as method of medical treatment while others rather accept claims worded as use claims and would then recognize the industrial applicability of these claims. Under the PCT Rules, no industrial applicability can be acknowledged. With regard to the above-cited claims, it should be noted that Rule 67.1 PCT is relevant insofar as independent claims 1 and 32 may define a use, but also include the treatment of cells which may

[ ] the description, claims or drawings *(indicate particular elements below)* or said claims Nos.
are so unclear that no meaningful opinion could be formed *(specify)* :

[ ] the claims, or said claims Nos. are so inadequately supported
by the description that no meaningful opinion could be formed *(specify)*:

[ ] no international search report has been established for said claims Nos.

[ ] a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

[ ] furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

[ ] a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[ ] See Supplemental Box for further details.

Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	6-8, 17, 26-31, 37-39, 48 and 49	YES
	Claims	1-5, 9-16, 18-25, 32-36 and 40-47	NO
Inventive step (IS)	Claims	6-8, 26-28 and 37-39	YES
	Claims	1-5, 9-25, 29-36 and 40-49	NO
Industrial applicability (IA)	Claims	13, 18 and 44	YES
	Claims		NO

2. Citations and explanations:

Prior Art Cited:

D1: WO 02/079183
D2: WO 01/24824
D3: WO 96/07431
D4: US 5,773,460
D5: *Blood*, 100(2) (15 July 2002), pp. 375-382
D6: *Blood*, 99(9) (1 May 2002), pp. 3083-3088
D7: *Photochem. Photobiol.*, 72(6) (2000), pp. 780-787

Summary of the Invention:

The present invention relates to the use of photodynamic therapy (PDT) in the treatment of immunologic disorders, infections and cancers. Central to the invention is the exposure of photoactivatable rhodamine derivatives to a sample of cells, which can later be reintroduced into the body. Cells that are activated tend to localize these compounds and result in the destruction of these cells once exposed to an activating (visible) light source, since the activated form of these compounds is very cytotoxic. The compounds are also known to have a low potential for DNA damage, mutation and/or carcinogenesis associated with their use. Cells that may be subject to this PDT include immune cells, infected cells and cancer cells. Destruction of the activated cells results in a release of antigen which is able to act as a vaccine upon reintroduction to the patient and initiates an immune response which, in turn, can effect the phrophylaxis and/or treatment of immunologic disorders, infection and cancers.

Summary of the Cited Art:

D1 discloses the production of rhodamine derivatives (including TH9402) that function as photosensitizers, and which preferentially localize in immunoreactive cells, where these cells can be subsequently destroyed by exposing them to visible light (PDT). The treatment may be in conjunction with an acceptable pharmaceutical carrier for the *ex vivo* elimination of reactive immune cells in patients with immunologic disorders. These rhodamines were found to be effective in preventing graft-versus-host disease (GVHD), and in the treatment of infections caused by Gram+ and/or Gram- bacteria, viral infections, leukemias, multiple myelomas and lymphomas, and solid tumours.

D2 discloses photoactivatable pharmaceutical compositions for the selective destruction of immunoreactive cells by using PDT in conjunction with a rhodamine derivative as photosensitizer (including TH9402). This was accomplished *ex vivo*, for the treatment of immunologic disorders, GVHD and organ rejection.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1, 22 and 32 still do not comply with Article 6 PCT. There is no apparent difference between preventing a disease and being protected from it, nor is there anything in the description to make this distinction. Clarification of the terms should thus be made.

Claims 13 and 44 are still unclear and thus do not comply with Article 6 PCT, despite the explanation forwarded by the applicant. Specifically, the method the applicant describes in his response to the Written Opinion describes a means by which the treatment is performed. This is not the issue. What is unclear is the use of "perfusion" in the claims, since that term is generally defined as the passage of fluid through a tissue or organ, or the bathing of an organ with said fluid. Claim 13, for example, would then define the use of claim 12, wherein the treatment is *ex vivo* and is effected by passing fluid (blood) through a tissue or organ. This does not appear to make sense. The treatment is said to be done outside the body (*ex vivo*) but the organ is inside the body and requires the use of the PDT machine (see the applicant's letter, page 8). Since the treatment is not done by passing the fluid through the tissue or organ, but rather by a PDT machine, followed by reinfusion of said fluid into the patient (see page 8 of the letter), the claim is presently misleading and should be reworded to more clearly define the subject-matter for which protection is sought.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

D3 discloses the synthesis of photosensitive rhodamine derivatives that are useful in PDT. Also disclosed is the preferential localization of these compounds in malignant cells, and their use in the treatment of tumours and in bone marrow purging for autologous transplantation.

D4 discloses photoactivatable rhodamine derivatives, including some of those encompassed by the present claims, for use in PDT. These derivatives were found to be preferentially localized in malignant cells, which lead to the selective destruction of these cells and lead to the *in vitro* treatment of tumours via the purging of cancerous clones in the bone marrow of chronic myelogenous leukemia (CML) patients.

D5 discloses that PDT of TH9402-exposed T-cells led to the selective elimination of immunoreactive T-cell populations, and determined that this can be applied to in the treatment of GVHD and other alloimmune and autoimmune disorders.

D6 discloses that mice injected with irradiated allologous spleen cells previously treated with TH9402 and exposed to visible light at 514 nm (photodynamic cell purging or PDP) allowed 90% of the recipients to remain tumour-free and free of GVHD for a 100 day observation period, and yet graft-versus-leukemia (GVL) activity is not impaired.

D7 discloses the use of the photosensitizer TH9402 and visible light in the PDT-mediated selective elimination of CML and breast cancer cells.

Novelty:

Specifically, claims 1-5, 9-16, 18-25, 32-36 and 40-47 are objected under Article 33(2) PCT as being anticipated by one or more of **D1** to **D7**. The relevant claims and reasoning for the objections being discussed below.

In his letter referring to the first Written Opinion, the applicant argued the relevance of the prior art cited in regard to the novelty of the present claims, indicating that there are distinct differences between the treatments as presently described, and those of the art.

There are three independent claims on file: claims 1, 18 and 32. Claim 1 is directed to the preparation of a medicament for the prevention, protection or treatment of an immunological disorder, infection and/or a cancer in an individual; claim 18 is directed to an immunologic vaccine; and claim 32 to a method for preparing an immunologic medicament for the prevention, protection from or treatment of an immunological disorder, infection and/or a cancer in an individual; all of said independent claims requiring the PDT-treatment of cells with one of the defined rhodamine derivatives.

In his dismissal of the prior art, the applicant raised a few issues that will be dealt with in turn. First, it was pointed out that claim 1 is directed to a new use of a medicament. It appears that the applicant is suggesting that this distinguishes the subject-matter of this claim from the art, which teach the use of PDT-treated cells for the treatment of identical diseases (*vide infra*). Claim 1 is in Swiss-claim format, but the underlying subject-matter is the use of PDT-treated cells for the stated purposes. It referring to a "medicament" does not make the claim novel over disclosures teaching the same use, but without directly using the term, nor is it clear how it is supposed to.

The second issue raised by the applicant is that the prior art treatment involved the use of chemotherapy and radiation in association with the PDT-treatment of the grafts, which is not required by the invention of the present application.

It is noted, however, that none of the present claims preclude the concomitant or sequential use of chemotherapy or radiation therapy, when used with grafts or otherwise. A vaccine can be broadly defined as a preparation containing whole or parts of disease-causing organisms used to induce immunity to said disease; an "immunologic medicament" can be exemplified by a vaccine, and is thus broader in scope. There is nothing in this definition that would distinguish the claimed invention over the prior art if the differences are merely in the use of the PDT-treated cells, as these claims do not exclude this possibility from their scope.

For example, claim 1 is essentially directed to the use of cells PDT-treated with a particular rhodamine derivative for the above-mentioned purposes. The other steps that are occurring during the actual medical administration of the medicament are irrelevant as the claim broadly encompasses the use of such treated cells in those capacities. It is not clear how the art does not apply simply because additional steps may be present when, or before, the PDT-treated cells are reintroduced into the patient. Similarly, it is irrelevant *why* the patient is being administered with the PDT-treated cells, since "immunologic medicament" appears to encompass the use of these cells in *any* immunologic capacity. Therefore, this cannot be used to render the prior art irrelevant. It is also worth mentioning that on page 31 and 32 of **D1**, the use of PDT in the treatment of cancers is outlined: use of chemotherapy and radiation therapy is preferred, but is not required.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Supplemental Box

It is further noted that although claim 18 is directed to a vaccine *per se*, claims 1 and 32 specifically refer to the use of PDT-treated cells for the treatment of the stated conditions. The treatment of these conditions extends beyond the common definition of vaccine and thus encompasses merely using these cells in some form in a treatment for certain conditions; it does not require that there be any future immunity afforded. Therefore, it is clear that even if the prior art merely mentions the use of cells PDT-treated using identical rhodamine derivatives in the treatment of the same conditions, that it will fall within the scope of these claims.

The applicant also raises the argument that the prior art only teaches one administration step, whereas the present invention is taught to be able to be administered multiple times. It is unclear how this is relevant. The claims do not require this, nor is it anything more than a preferred embodiment. The prior art does not teach that multiple administrations cannot be done, but suggests that multiple administrations *need* not be done to achieve the desired result.

Another of the applicant's rebuttals that is used to base many of his arguments was that it is common practice to wash the PDT-treated cells, removing the dead cells and debris from the sample prior to reintroduction. This would effectively remove the material responsible for the result obtained from the present invention. It is noted that there was nothing found to support this position in any of **D1** to **D7**. It is clear from the examples of **D1**, for example, that the only washing that is done is after infusing the cells with the rhodamine derivatives. There is no mention of washing after PDT-treatment, nor the removal of any material. The applicant argues that this is what is done in the art but, although the washing step after the *dyeing* is explicitly mentioned, there is conspicuously no mention of the lavage step the applicant refers to. It is thus clear that the dead cells, debris etc. are still present in the sample, and are therefore reintroduced with the living cells. There is also nothing in these documents that would indicate that such a step is done or would be desirable. While it may be common practice in certain circumstances, it is clear that such a washing step was not present in **D1** to **D7**, making these documents prejudicial to the novelty of claim 1. Claim 32 is also anticipated as the method is identical to those used in the art for such treatments (or medicament preparations).

It is acknowledged that the concept of a vaccine is unique to the present invention, with the exception of **D1**. Therefore, claim 2 is only deemed anticipated by this art. However, this is based on "vaccine" referring to the prevention of disease only. If the term is extended to include treatment, then all of **D1** to **D7** apply, since they all teach the reinfusion of the cells, dead or otherwise, from the PDT making them the equivalent of a vaccine for the treatment of the disclosed diseases.

In respect of claims 3, 4 and 33-35, the applicant argues that the reinfused cells excluded the immunoreactive T cells, to only include resting cells. Again it is mentioned that the "customary lavages" would result in the relevant materials being removed making the medicaments different than those of the present invention. There is no evidence to support that this lavage step was actually done, however, in **D1**, **D2**, **D5** and **D6** so this argument is baseless.

The objections to these claims as well as 5 and 36 are thus also maintained.

The novelty objection to claims 6, 7, 37 and 38 has been withdrawn, as it is noted that **D1** uses the rhodamine derivatives as a means for treating bacterial or viral infections, and not the PDT-treated *cells* themselves as required by the present claims.

Since there does not appear to be support for the applicant's assertion that there is a lavage step in the art that would change the composition of the medicament in relation to that of claims 9-11 and 40-42, the objection against these claims is maintained (see **D1**, **D3**, **D4** and **D7**).

Claims 12-16 and 43-47 were argued to be novel because the use of the rhodamine derivatives is new. Since the applicant's arguments regarding the novelty of the use are not convincing for the reasons mentioned, these claims are still deemed anticipated by **D1** to **D7**.

With respect to claims 18-25: since there is no support for the contention that the dead cells and fragments are indeed removed from the PDT-treated aliquots, these components would still be present upon reinfusion into the patient, and would thus act as a vaccine. In fact, it is noted that the treatment of immunologic diseases such as GvHD (graft vs. host disease) and autoimmune diseases on pages 33 and 34 of **D1** are suggestive of vaccination without using this term explicitly. In order to prevent GvHD, for example, the inventors indicate that the patient and donor's cells are mixed until an immune reaction occurs. The PDT is then performed and the cells reinserted in the patient. The PDT destroys the activated cells, releasing cellular components of the dead cells into the mixture. When this is reinserted in the patient, it will effect a vaccination to prevent an immune response when the graft is performed (i.e. prevent GvHD). A similar protocol is described for autoimmune reaction prevention. It is thus clear that, at least in regard to immunologic diseases, that the inventors of **D1** taught the use of PDT-treated cells as vaccines. Claims 26 and 29-31 were dropped from this objection because it is acknowledged that **D1** does not teach the use of such treated cells in the manufacture of a vaccine (see definition proviso

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Supplemental Box

It is acknowledged that the application does contain patentable subject-matter: for example, if the reference to treatment were excluded from the claims, then vaccination against cancers and infections would be considered novel, as none of the cited art teaches these uses. In relation to the others, however, the features to which the applicant refers in attempting to establish novelty are currently not present in the claims, and thus cannot be used to distinguish the invention over the prior art. If these features are not introduced into the claims and the applicant chooses to argue the novelty of the present claims instead, then the features *in those claims,* which distinguish them from the prior art, should be referred to. Features which do not form part of the claims cannot be drawn upon to establish novelty, as the scope of the claims encompass much broader subject-matter (including the prior art) in their absence. For instance, the present claims do not require specific cells to be used or that the PDT-treated cells are only intended for use when no other chemiotherapy or radiotherapy is being administered, and therefore cannot be relied upon to establish the novelty of the claims. It would also be helpful for any remarks made about the relevance of the prior art to be accompanied by references to specific paragraphs therein upon which the argument is based (e.g. where it is taught that the PDT-treated cells are washed prior to reinfusion in the patient).

Presently, novelty can be acknowledged for the subject-matter of claims 6-8, 17, 26-31, 37-39, 48 and 49.

Inventive Step:

Claims 1-5, 9-16, 18-25, 32-36 and 40-47 are considered to lack an inventive step under Article 33(3) PCT in light of the fact that they were found to be anticipated by the art.

Claims 17-25, 29-31, 48 and 49 are also considered uninventive in light of the art. The applicant argued all the objections under this Article; however, his reasons were not persuasive in some cases.

The objection to a lack of inventive step for claims 8, 28 and 39 are withdrawn, as it is acknowledged that the art does not teach, nor suggest, the use of PDT-treated cells themselves for the prevention, or treatment of infections.

Claims 17 and 48 were objected to as lacking an inventive step over the art, especially **D1** to **D4**. The applicant agreed with the examiner's assessment that using antigen-presenting cells in conjunction with immunising antigens is known. The only argument against the objection relies on the alleged washing step that would remove the material responsible for the result. Since no evidence of such a washing step was found in the art, this objection is maintained.

The applicant also argued the objections made to claims 18-22, averring that the carriers in **D2** to **D4** are oriented toward stabilisers, whereas those of the present application are directed to a substance that would promote the immunisation process, and that they are therefore non-obvious variants. The examiner notes, however, that the term "carrier" is simply a vehicle for the active ingredient, as the term is used in the art. Although the applicant may prefer to use compounds/materials which promote immunisation, the use of "carrier" in these claims is much broader than this interpretation. Presently, and as would be understood by a person skilled in the art, the term encompasses physiologically tolerated vehicles (solvents etc.) The scope of the term is thus much broader than the interpretation given by the applicant. It is further noted that carriers are well known in the art, simply adding one to an active agent is not considered inventive unless some unexpected technical benefit is derived from doing so. The objection is therefore maintained.

In light of the above arguments, the objections to claims 23-25 and 29-31 are similarly not withdrawn.

Newly-submitted claim 49 is also deemed uninventive in light of the art. Although there may be no explicit mention in the art of the procedure of PDT-treated cell administration being repeated, a person skilled in the art would know to do so if deemed appropriate.

In their present form, an inventive step *can* be acknowledged for claims 6-8, 26-28 and 37-39.

Industrial Applicability:

Claims 13, 18 and 44 comply with Article 33(4) PCT as being related to industrially useful subject-matter.